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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/894,845 | 06/27/2001 | Xavier Paliard | 1681.002 | 3705 |

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| EXAMINER | |
|---|---|
| ANGELL, JON E | |

| ART UNIT | PAPER NUMBER |
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| 1635 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/894,845 | PALIARD, XAVIER | |
| | Examiner | Art Unit | |
| | J. E. Angell | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,6,7,10-12,15-21,41 and 43-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6, 7, 10-12, 15-21, 41, 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This Action is in response to the communication filed on 4/15/2008.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

### *Status of the Claims*

Claims 1-3, 6, 7, 10-12, 15-21, 41, 43-45 are currently pending and are addressed herein.

It is noted that an election of species was required and Applicants' election of a species in their 4/15/2008 communication is acknowledged. It is noted that upon searching for the elected species, the non-elected species was identified in the same reference. Accordingly, the species election is now considered moot. Therefore, the election of a single species is hereby withdrawn and all of the pending claims are examined herein.

It is noted that Applicants have amended claim 1 to include the new limitation that the method results in liver-specific expression of the HCV immunogen. Furthermore, new claims 43-45 have been added which specify the element(s) that regulate the liver-specific expression. The amendments overcome the rejections of record; however, a new grounds for rejection are set forth herein.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 6, 7, 10-12, 15-19 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorczynski et al. (Cellular Immunology, 1995, cited by Applicants) in view of U.S. Patent No. 6,582,692 (Podsakoff et al.), and further in view of Wakita et al. (JBC, 1998, cited by Applicant).

Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorczynski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorczynski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal (e.g., see Podsakoff et al.). Furthermore, the prior art also recognizes that a transgenic animal that expresses specific HCV genes in its liver can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection. (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice and as long as the transgene was present it would be expressed in the animal).

Podsakoff et al. specifically teach the sustained expression of a gene of interest in the liver of an animal using an adeno-associated viral vector that expresses the gene of interest using the liver-specific alpha-1 antitrypsin promoter and ApoE enhancer wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., Figure 5; Figures 10-12; column 7, lines 51-61; column 8, lines 23-38; etc.). It is noted that Podsakoff et al. show that the AAV-ApoE/hAAT-hGC vector injected by tail vein injection resulted in the expression of hGC 4 weeks after the injection (e.g., see Figure 11 and column 8, lines 29-34).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a transgenic mouse results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to an HCV gene (i.e., HCV E1 or HCV E2) can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings based on the teaching of Wakita that an animal that expresses an HCV transgene in the liver of an animal results in an animal that is "a powerful tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract of Wakita). Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier

way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

Claims 1-3, 6, 7, 10-12, 15-21 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorczynski et al. (Cellular Immunology, 1995, cited by Applicants) in view of U.S. Patent No. 6,582,692 (Podsakoff et al.), further in view of Wakita et al. (JBC, 1998, cited by Applicant) and further in view WO 97/47358 (Donnelly et al.), for the reasons of record (e.g., see 10/18/2005 Office Action) which are reiterated herein for convenience.

As indicated above, Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorczynski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorczynski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal. Furthermore, the prior art also recognizes that a transgenic animal that expresses specific HCV genes in its liver can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection. (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice and as long as the

transgene was present it would be expressed in the animal), and the HCV NS5a gene was recognized in the prior art as an HCV gene which could be used to raise an immunological response to HCV in an animal (e.g., see Donnelly et al.).

Podsakoff et al. specifically teach the sustained expression of a gene of interest in the liver of an animal using an adeno-associated viral vector that expresses the gene of interest using the liver-specific alpha-1 antitrypsin promoter and ApoE enhancer wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., Figure 5; Figures 10-12; column 7, lines 51-61; column 8, lines 23-38; etc.). It is noted that Podsakoff et al. show that the AAV-ApoE/hAAT-hGC vector injected by tail vein injection resulted in the expression of hGC 4 weeks after the injection (e.g., see Figure 11 and column 8, lines 29-34).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a transgenic mouse results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Donnelly specifically teaches a nucleic acid encoding the HCV NS5a gene (e.g., see Figure 12) which can be used to raise an immunological response to HCV in animal (e.g., see page 1, lines 16-21; page 3, lines 17-31; page 10, line 31 through page 1 line 35; page 20, lines 14-17; claims 1, 2, 15; etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to the HCV NS5a gene can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings and make the HCV NS5a tolerant animal based on the teaching of Wakita that an animal that expresses an HCV transgene in the liver of an animal results in an animal that is "a powerful tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract of Wakita), and also in view of the teaching of Donnelly that HCV NS5a is a specific immunogenic HCV gene. Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

### *Response to Arguments*

Applicant's arguments and the Declaration of Dr. Houghton filed 11/1/2007 are acknowledged. The amendment to the claim has overcome the previous rejections. The instant rejections are new grounds of rejections which rely on a new reference (Podsakoff et al.) and which do not require a previously cited reference (Nakai et al.). Applicant's arguments and the Declaration do not specifically address the new rejections. The instant rejection is made after filing of a "Request for Continued Examination" (RCE), as such the instant Office Action is made Non-Final.

### *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on 9:00 a.m. - 5:00 p.m. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner, Art Unit 1635